149. (New) The method of Claim 148 wherein

(1) the fusion protein in (a) comprises an Fc domain;

(2) the fusion protein in (b) comprises an Fc domain; or

(3) both (1) and (2).

a8 Cont

150. (New) The method of Claim 148 wherein

(1) the fusion protein in (a) comprises an Fc domain of an IgG molecule;

(2) the fusion protein in (b) comprises an Fc domain of an IgG molecule; or

(3) the fusion protein in (a) and (b) comprises an Fc domain of an IgG molecule.

Addc11

REMARKS

Claims 1-44 and 51-76 have been cancelled, Claims 45-50 have been amended, and Claims 77-150 have been added. No new matter has been added. Claims 45-50 and 77-150 are pending.

Amendments to the Specification

At page 6, line 18, "ligands" has been deleted and "ligand" has been inserted therefor.

At page 10, line 4, "of" has been inserted between "all" and "its".

At page 13, line 25, "the" has been deleted.

At page 17, line 28, "veinous" has been deleted and "venous" has been inserted therefor.

At page 18, line 7, "cells" has been deleted and "cell" has been inserted therefor.

At page 23, lines 7 and 10, "Eph4" has been deleted and "EphB4" has been inserted therefor. Support for the recitation of "EphB4" is found throughout the specification, for example, at page 7, lines 26-27.

At page 32, line 6, "was" has been deleted.

Amendments to the Claims

Support for the recitation "agent" in amended Claims 45-50 is found, for example, in the specification at page 16, line 19 to page 17, line 25.

Claims 46, 47, 49 and 50 have been redrafted as independent claims. Support for the recitation "Ephrin family ligand or a portion thereof" and "Eph family receptor or portion

thereof" in Claims 46 and 49 is found, for example, in the specification at page 18, line 24 to page 19, line 10. Support for the recitation "EphrinB2 or a portion thereof" and "EphB4 or a portion thereof" in Claims 47 and 50 is found, for example, in the specification at page 18, line 24 to page 19, line 10.

Support for new Claims 77-150 is found, for example, in the specification at page 16, line 19 to page 19, line 19.

The amendments to the specification and claims and new Claims 77-150 are supported by the parent application as originally filed. Therefore, this Amendment adds no new matter.

Reply to Restriction Requirement

Responsive to the Restriction Requirement dated November 2, 2001, the claims of Group VIII (Claims 45-50) drawn to drug screens are elected for prosecution. Applicants reserve the right to file a continuing application or take such other appropriate action as deemed necessary to protect the non-elected inventions. Applicants do not hereby abandon or waive any rights in the non-elected inventions.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 6, lines 15-26 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

As described in the examples, a gene which encodes a cell membrane-associated ligand which is present in the nervous system and the vascular system has been shown, in adult mice, to be expressed by arterial endothelial cells, and not by venous endothelial cells. Further, the gene which encodes the receptor for the [ligands] ligand has been shown to be expressed by venous endothelial cells, but not by artery cells. Thus, for the first time, a marker found on arterial endothelial cells (an artery-specific marker) and a venous endothelial cell- (vein-specific) marker are available, making it possible to distinguish between arteries and veins for a variety of purposes, such as further study and understanding of the mechanisms of blood vessel formation; selective targeting of treatments or therapies to arteries or veins (targeting to arteries but not veins or vice versa) and selective modulation (enhancement or inhibition) of formation, growth and survival of arteries and/or veins.

Replace the paragraph at page 10, lines 3-7 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

As used herein, a transgenic mouse is one which has, incorporated into the genome of some or all of its nucleated cells, a genetic alteration which has been introduced into the mouse or at least one of its ancestors, by the manipulations of man. A transgenic mouse can result, for example, from the introduction of DNA into a fertilized mouse ovum or from the introduction of DNA into embryonic stem cells.

Replace the paragraph at page 13, line 18 through page 14, line 9 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

As a result of the work described herein, it is possible to differentiate between arterial endothelial cells (arteries) and venous endothelial cells (veins) by taking advantage of the presence of an artery-specific or vein-specific gene product on the surface of the cells. Arterial endothelial cells and venous endothelial cells can each be isolated from cells of other tissue types by, for instance, excision of artery or vein tissue from a sample of mammalian tissue, dissociation of the cells, allowing the cells to bind, under appropriate conditions, to a substance which has some property or characteristic (e.g., a molecule which provides a label or tag, or molecule that has affinity for both [the] an artery-specific cell surface protein and another type of molecule) that facilitates separation of cells bound to the substance from cells not bound to the substance. Separation of the cells can take advantage of the properties of the bound substance. For example, the substance can be an antibody (antiserum, polyclonal or monoclonal) which has been raised against the protein specific to arterial endothelial cells (or to a sufficiently antigenic portion of the protein) and labeled with a fluorochrome, with biotin, or with another label. Separation of cells bound to the substance can be by fluorescence activated cell sorting (FACS), for a fluorescent label, by streptavidin affinity column, for a biotin label, by other affinity-based separation methods, or, for example, by antibody-conjugated magnetic beads or solid supports. "Isolated" as used herein for cells indicates that the cells have been separated from other cell types so as to be a population enriched for a certain cell type, compared to the starting population, and is not limited to the case of a population containing 100% one cell type.

Replace the paragraph at page 17, line 26 through page 18, line 12 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

A drug that inhibits interaction of an artery-specific cell surface molecule (e.g., an arterial endothelial cell-specific surface molecule) with a vein-specific cell surface molecule (e.g., a venous endothelial cell-specific surface molecule) can be identified by a method in which, for example, the arterial endothelial cell-specific surface molecule and the [veinous] venous endothelial cell-specific surface molecule are combined with a drug to be assessed for its ability to inhibit interaction between the cell-specific molecules, under conditions appropriate for interaction between the cell-specific molecules. The cell-specific molecules may be used in the assay such that both are found on intact cells in suspension (e.g., isolated arterial or venous endothelial cells, immortalized cells derived from these, or cells which have been modified to express an artery- or vein-specific [cells] cell surface molecule); one cell type is fixed to a solid support, and the other molecule, specific to the other cell type, is in soluble form in a suitable solution; or the molecule specific to one cell type is fixed to a solid support while the molecule specific to the other cell type is found free in a solution that allows for interaction of the cell-specific molecules. Other variations are possible to allow for the convenient assessment of the interaction between the two different cell-specific molecules.

Replace the paragraph at page 23, lines 7-23 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The differential expression of EphrinB2 in arteries and of [Eph4] EphB4 in veins allows for the specific targeting of drugs, diagnostic agents, imaging agents, or other substances to the cells of arteries or of veins. A targeting vehicle can be used for the delivery of such a substance. Targeting vehicles which bind specifically to EphrinB2 or to [Eph4] EphB4 can be linked to a substance to be

delivered to the cells of arteries or veins, respectively. The linkage can be via one or more covalent bonds, or by high affinity non-covalent bonds. A targeting vehicle can be an antibody, for instance, or other compound which binds either to EphrinB2 or to EphB4 with high specificity. Another example is an aqueously soluble polypeptide having the amino acid sequence of the extracellular domain of EphB4, or a sufficient portion of the extracellular domain (or a polypeptide having an amino acid sequence conferring a similar enough conformation to allow specific binding to EphrinB2), which can be used as a targeting vehicle for delivery of substances to EphrinB2 in arteries. Similarly, a soluble polypeptide having the amino acid sequence of the extracellular domain of EphrinB2 or a sufficient antigenic portion of the extracellular domain (or a polypeptide having an amino acid sequence conferring a similar enough conformation to allow specific binding to EphB4), can be used to target substances to EphB4 in veins.

Replace the paragraph at page 32, lines 6-11 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Defects in yolk sac angiogenesis [was] were apparent by E9.0 and obvious at E9.5. There was an apparent block to remodeling at the capillary plexus stage, for both arterial vessels, as revealed by β-galactosidase staining, and venous vessels in the anterior region of the sac, as revealed by PECAM staining. Thus, disruption of the *EphrinB2* ligand gene caused both a non-autonomous defect in EphB4 receptor-expressing venous cells, and an autonomous defect in the arteries themselves.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Claims 1-44 and 51-76 have been cancelled and Claims 77-150 have been added.

45. (Amended) A method for identifying [a drug] an agent that inhibits interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, comprising:

(a) combining:

(1) the arterial cell-specific surface molecule;

(2) the venous cell-specific surface molecule; and

(3) [a drug] the agent to be assessed for its ability to inhibit interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

(b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the [drug] agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);

wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is less in the presence of the [drug] agent than in the absence of the [drug] agent, the [drug] agent is one which inhibits interaction of the arterial cell-specific molecule of (1) with the venous cell-specific molecule of (2).

46. (Amended) [The] A method [of Claim 45] for identifying an agent that inhibits interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, wherein the arterial cell-specific surface molecule is an Ephrin family ligand or a portion

thereof and the venous cell-specific surface molecule is an Eph family receptor or a portion thereof, comprising:

(a) combining:

(1) the Ephrin family ligand or a portion thereof;

(2) the Eph family receptor or a portion thereof; and

(3) the agent to be assessed for its ability to inhibit interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

(b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);

wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is less in the presence of the agent than in the absence of the agent, the agent is one which inhibits interaction of the arterial cell-specific molecule of (1) with the vein cell-specific molecule of (2).

47. (Amended) [The] A method [of Claim 46 wherein the Ephrin family ligand] for identifying an agent that inhibits interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, wherein the arterial cell-specific surface molecule is EphrinB2 or a portion thereof and the venous cell-specific molecule [Eph family receptor] is EphB4 or a portion thereof, comprising:

(a) combining:

(1) EphrinB2 or a portion thereof;

(2) EphB4 or a portion thereof; and

(3) the agent to be assessed for its ability to inhibit interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

(b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);

wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is less in the presence of the agent than in the absence of the agent, the agent is one which inhibits interaction of the arterial cell-specific molecule of (1) with the vein cell-specific molecule of (2).

48. (Amended) A method for identifying [a drug] an agent that enhances interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, comprising:

(a) combining:

(1) the arterial cell-specific surface molecule;

(2) the venous cell-specific surface molecule; and

(3) [a drug] the agent to be assessed for its ability to [inhibit] enhance interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

(b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the [drug] agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);

wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is greater in the presence of the [drug] agent than in the absence of the [drug] agent, the [drug] agent is one which enhances interaction of the arterial cell-specific molecule of (1) with the venous cell-specific molecule of (2).

49. (Amended) [The] A method [of Claim 48] for identifying an agent that enhances interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, wherein the arterial cell-specific surface molecule is an Ephrin family ligand or a portion thereof and the venous cell-specific surface molecule is an Eph family receptor or a portion thereof, comprising:

(a) combining:

(1) the Ephrin family ligand or a portion thereof;

(2) the Eph family receptor or a portion thereof; and

(3) the agent to be assessed for its ability to enhance interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

(b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);